REMARKS

Claims 1-7, 9, 11 and 14 are pending. By virtue of this response, claims 1, 2, and 5 are amended, and claims 16-19 are added. Therefore, claims 1-7, 9, 11, 14, and 16-19 are presently pending. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. No new matter is added.

Support for the amendments to claims 1 and 5 can be found throughout the specification including, by way of example, on page 2, lines 17-25 of the specification. Support for new claims 16-19 similarly can be found throughout the specification including, by way of example, on page 2, lines 17-25 of the specification. Claim 2 has been amended as suggested by the Examiner.

I. New Claim Objections under 35 USC § 112 - Second Paragraph

The Examiner has objected to claims 1 and 5 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation "sequence."

Applicants respectfully traverse the rejection and its supporting remarks. However, to facilitate prosecution, Applicants have amended the claim to recited "sequence identity". The amendment does not change the scope of the claim, because one of skill in the art would never interpret "identity" as "percent functional identity" since there simply is no such concept in the biological sciences.

Applicants therefore respectfully request that the Examiner withdraw the objection to claims 1 and 5.

The Examiner has objected to claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation "and/or."

Applicants have amended claim 2 to recite "or".

Applicants therefore respectfully request that the Examiner withdraw the objection to claim 2.

II. Maintained-Double Patenting Rejection

The Examiner has provisionally rejected claims 1-7, 9, and 11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 28, 36, 45, and 46 of *Masignani et al.* (US Application No.: 10/472,681).

Applicants have amended independent claims 1 and 5. In view of the current claim amendments and the discussion below Applicants respectfully renew their request that the Examiner hold this rejection in abeyance until such time as there is an indication of otherwise allowable subject matter. Only at that time will Applicants be able to determine whether an obviousness-type double patenting rejection is applicable, and at such time Applicants may amend 10/472,681 to remove such claims if necessary.

III. Claim Rejections Under 35 USC §112 – First Paragraph

Maintained-Enablement

The Examiner has maintained his rejections of claims 1-3, 5-7, 9, and 11 under 35 U.S.C. 112, first paragraph, as allegedly not providing enablement for any mutant *Neisseria meningitidis* (*N. meningitidis*) ADP-ribosylating protein or fragments thereof with any substitution at Glu-109, or Glu-111, or Glu-120.

Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, Applicants have amended independent claims 1 and 5 to recite " … at least 90% sequence identity to SEQ ID NO: 1, …" and assert that those skilled in the art would not have to embark in undue experimentation in order to practice the invention.

The Examiner points to scientific publications that are unrelated to *N. meningitidis* ADP-ribosyl transferases, but suggest that limited mutagenesis of **enzymes** can affect respective **enzyme activities**. The present invention, however, does not seek to modify enzyme activities in a subtle manner, as *e.g.* described by *Witkowski et al.* (Biochemistry 38:11643-11650, 1999) for β-ketoacyl synthases, or seek to predict enzymatic function from a polypeptide's primary structure, as discussed in *Whisstock et al.* (Q. Rev. Biophys. 36: 307-40). Instead, the invention aims to achieve the much simpler task of disrupting enzymatic function, regardless of whether the three-dimensional structure of the wild-type polypeptide is maintained in the resulting mutant or not. The specification discloses, and claim 1 recites, four positions in SEQ ID NO: 1 where amino acid substitutions will have this desired effect (*see, e.g.,* page 35, lines 9-11 and Fig. 4). A person with skill in the art would expect that additional amino acid substitutions are likely to introduce further disruptions. The Examiner has pointed out the theoretical possibility that among the many known or unknown strains of *N. meningitides* there may be individual strains carrying homologues of SEQ ID NO: 1 which do not share the same mechanism as the enzymes disclosed in the application at issue. However, the Examiner has been unable to point out any such strain or polypeptide with particularity. Applicants respectfully assert that the mere hypothetical possibility that polypeptides could exist that do not follow the mechanism disclosed in this application does not render the experimentation required to practice the invention at hand undue.

One of the preferred uses of this invention is the application of ADP-ribosylating toxins of *N. meningitidis* as adjuvants, *i.e.* as general boosters of specific immune reactions targeted against other immunogens, including immunogens that are structurally and functionally unrelated to polypeptides comprising SEQ ID NO: 1 (page 2, lines 3-15). A person of ordinary skill would understand that the *in vivo* adjuvant activity of a polypeptide is much less dependent on its three dimensional structure than its enzyme activity or its ability to bind a specific monoclonal antibody. Molecular structures as diverse as unmodified polypeptides, purified lipopolysaccharides (LPS), or crude bacterial membrane preparations (Freud's adjuvant) are known to raise potent and selective immune responses against immunogens that are structurally unrelated to the co-administered adjuvant. Importantly, the specification discloses four adjuvants containing ADP-ribosylation

activity, including diphtheria toxin, exotoxin A, heat-labile enterotoxin, pertussis toxin, and ADP-ribosylating toxin from *N. meningitidis* (see, e.g., page 1, lines 6-8 and page 1, lines 20-34). A person of skill would therefore expect that the chances of maintaining adjuvant activity after iteratively introducing point mutations into a given polypeptide are very high, regardless of the mutations' effect on the polypeptide's three-dimensional structure. One molecular theory underlying this general expectation is that a polypeptide's adjuvant effect is not dependent on the immune system's recognition of any given epitope. Instead, he adjuvant effect is merely dependent on the immune system's recognition of the polypeptide as a foreign structure. Different structural features of a mutant and a wild-type protein can therefore mediate the adjuvant activity of the polypeptide. The immune system has evolved to distinguish a plethora of structural features as foreign and to respond accordingly.

The Federal Circuit held in *In re Wands* that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d 731, 737 (Fed.Cir. 2008); MPEP 2164.06. Similar to *Wands*, the present application provides working examples and ample guidance for making and testing mutants of *N. meningitides* ADP-ribosylating proteins comprising SEQ ID NO: 1. The execution of these experiments is merely routine, and therefore not undue experimentation. Moreover, in the case of *Wands*, the chances of finding Hepatitis B reactive antibodies were low with respect to each individual hybridoma supernatant, but the overall chances of finding antibodies of the desired quality in the course of a laborious screening experiment were high. Similarly, here, the chances of identifying additional mutants or fragments of ADP-ribosylating *N. meningitides* proteins through mere routine experimentation are very high (MPEP 2164.06(b)). Applicants therefore assert that the current specification enables the use of polypeptides having at least 90% sequence identity to SEQ ID NO: 1, as recited in amended independent claims 1 and 5, and the use of polypeptides having at least 95%, or 99% sequence identity to SEQ ID NO: 1, as recited in new claims 16 to 19.

In conclusion, Applicants assert that using the invention as currently claimed does not require undue experimentation and request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, enablement.

Maintained-Written Description

The Examiner has maintained his rejection of claims 1-3, 5-7, 9, and 11 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks. The Written Description Training Materials prepared by the USPTO (Revision 1, dated March 25, 2008), provides a clear example that shows that the pending claims meet the written description requirement. The language of the pending independent claims 1 and 5 is very similar to the language in claim 1 of Example 11:

> Claim 1. An isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO: 2.

The training materials indicate that the exemplary claim 1 satisfies the written description requirement because:

> "With the aid of a computer, one of skill in the art could have identified all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2. Thus, one of ordinary skill in the art would conclude that the applicant was in possession of the claimed genus at the time the application was filed."

Since the pending claims as rejected by the Examiner recite a polypeptide having a percent sequence identity to a reference SEQ ID NO and do not claim an activity for the recited polypeptide (as in claim 2 of Example 11 of the Guidelines), the presently pending claims meet the written description guidelines.

Applicants therefore respectfully request that the Examiner withdraw the rejections under 35 U.S.C. 112, first paragraph, written description.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002103000**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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